Remarks

Claims 1-20 were pending in the subject application. By this Amendment, claims 1, 3-5, 9, and 10 have been amended, and claims 2, 6, and 11-20 have been cancelled. The undersigned avers that no new matter is introduced by this amendment. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 1, 3-5, and 7-10 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

Claims 1-10 have been rejected under 35 U.S.C. §112, first paragraph, as non-enabled. The applicants respectfully submits that the subject specification fully enables the claimed invention. The applicant submits that, given the benefit of the specification, one of ordinary skill in the art can determine analogues of metanicotine, nAChR antagonists, mixed nAChR agonists/antagonists, and neurological conditions characterized by dysfunction of nicotinic acetylcholine receptors without resort to undue experimentation. However, by this Amendment, the applicant has amended the claims to expedite prosecution and to lend greater clarity to the claimed subject matter.

Claim 1 has been amended to recite that the compound co-administered with metanicotine or a pharmaceutically acceptable salt thereof is selected from the group consisting of acetylcholine; nicotine; 3-[2,4-dimethoxybenzylidene]-anabaseine (GTS-21); 2-methyl-3-(2-(S)-pyrrolidinyl methoxy)pyridine (ABT-089); (S)-3-methyl-S-(1-methyl-2-pyrrolidinyl)isoxazole (ABT-418); (R)-5-(2-azetidinyl-methoxy)-2-chloropyridine (ABT-594); altinicline (SIB-1508Y); (±)-4-{[2-(1-methyl-2-pyrrolidinyl) ethyl]thio}phenol hydrochloride (SIB-1553A); epibatadine; and mecamylamine; or a pharmaceutically acceptable salt of any of the foregoing. As indicated at page 10, paragraph 0027 and paragraph 0028, of the specification, receptor specificities for the recited compounds have been described in the scientific literature. Furthermore, claim 1 has been amended to recite that the neurological condition is selected from the group consisting of Alzheimer's disease, Parkinson's disease, Huntington's chorea, tardive dyskinesia, hyperkinesias, mania, attention deficit disorder, attention deficit hyperactivity disorder, sleep-wake disorder, chronic-fatigue syndrome, tremor, epilepsy, neuropathic pain, addiction, anxiety, dyslexia, schizophrenia, obsessive-compulsive disorder and Tourette's syndrome, or combinations of any of the foregoing. Support for these

amendments can be found, for example, at page 10, paragraph 0027, pages 11-12, paragraph 0032, and page 14, paragraph 0038, of the specification, and claims 2 and 6 of the application as originally filed.

At pages 2, 3, and 6, the Office Action acknowledges that the subject specification provides sufficient information to enable using the combination of metanicotine, or a pharmaceutically acceptable salt thereof, and the antagonists and mixed agonists/antagonists specifically exemplified in the specification (*e.g.*, acetylcholine, nicotine, GTS-21, ABT-089, *etc.* ...) to treat those neurological conditions specifically exemplified in the specification (Alzheimer's disease, Parkinson's disease, Huntington's chorea, *etc.*, ...). Therefore, the applicant respectfully submits that the claimed invention is fully enabled by the subject specification. In view of the foregoing remarks and the amendments to the claims, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

Claims 1-10 have been rejected under 35 U.S.C. §103(a) as being obvious over Crooks *et al.* (U.S. Patent No. 5,616,707) and further in view of Newhouse *et al.* (*Society of Biological Psychiatry*, 2001, 49:268-278). The applicant respectfully submits that the claimed invention is not obvious over the cited references.

Submitted herewith is a Declaration by Dr. Roger Papke under 37 C.F.R. §1.132. As Dr. Papke states, it has been shown that metanicotine selectively activates the high affinity alpha4beta2 nAChR subtype, with little agonist activity on the alpha7 subtype (Papke RL, *et al.*, *J. Neurochem.*, 75(1):204-16, July 2000, submitted herwith). "Although metanicotine was once proposed to be a potential drug for the treatment of AD (as indicated in the Crooks *et al.* patent), recent studies have suggested that the appropriate molecular target for this indication is in fact the alpha7 receptor (Kem WR, *Behav. Brain. Res.*, 113(1-2):169-181, August 2000, submitted herewith), which metanicotine does not effectively stimulate." Papke Declaration, page 14, line 29 through page 15, line 5. Thus, based upon what was known of metanicotine's activity from the scientific literature at the time the subject patent application was filed, there would be no motivation to administer metanicotine for treatment of Alzheimer's disease (AD), by itself or in combination with the other recited compounds. As the Examiner is aware, in order to support a *prima facie* case of obviousness, a person of ordinary skill in the art must find both the suggestion of the claimed invention, and a reasonable expectation

of success in making that invention, in light of the teachings of the prior art. *In re Dow Chemical Co.*, 5 USPQ 2d 1529, 1531 (Fed. Cir. 1988).

Moreover, while their activity on alpha7 receptors makes ABT-418 and GTS-21 candidate drugs for AD, their usefulness would be limited by their residual antagonist activity, which restricts their effectiveness on alpha7 receptors and potentially would compromise other functions mediated by non-alpha7 receptors in the brain and peripheral nervous system, thereby demonstrating a need which the instant invention addresses. As described in Example 5 of the subject application, Figures 6A and 6B show results obtained when oocytes expressing alpha3beta4 or alpha3beta4 (6'F10'T) receptors were treated with DMXB alone or in the presence of QX-314, tetracaine, or metanicotine (TC-2403). The experimental data was also published in the Papke publication (*J. Pharmacol. Exp. Ther.*, 301(2):765-773, 2002), which is submitted herewith. As Dr. Papke explains,

> the data in the subject patent application shows that the combination of metanicotine with compounds that are nAChR antagonists or mixed agonists-antagonists, such as ABT-418 and GTS-21, likely have a synergistic (*i.e.*, far more than additive) effect through the ability of metanicotine to diminish the otherwise concomitant antagonist activity of the other cholinergic antagonist or mixed agonist-antagonist. As demonstrated in Example 5 and Figures 6A and 6B of the subject patent application and the Papke (2002) publication (*J. Pharmacol. Exp. Ther.*, 301(2):765-773, 2002), which is submitted herewith, only co-application of metanicotine was effective at decreasing residual inhibition by mixed agonists-antagonists and protecting receptor function. This effect was not observed by the other agents tested (the local anesthetics QX-314 and tetracaine). Moreover, this ability of metanicotine to protect nAChR function from long-term inhibition by antagonists or mixed agonists-antagonists was not previously recognized in the scientific literature, and would not have been expected based upon the individual activities of metanicotine and the other compounds.

As demonstrated by the experimental data in the subject application, treatment with metanicotine actually decreased the residual inhibition otherwise exhibited by mixed agonists-antagonists. As Dr. Papke indicates, this property would not have been predicted based on the compounds' effects on nAChR function individually. Thus, the co-administration of metanicotine and the recited compounds has a synergistic effect and this interaction is unexpected in view of the activities of the individual compounds. It is well settled in patent law that "a greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness ... of the claims at issue" *In re Corkill*, 226 USPQ 1005 (Fed. Cir. 1985). Evidence of a greater than expected result

may be shown by demonstrating an effect which is greater than the sum of each of the effects taken separately (*i.e.*, demonstrating "synergism"). *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied*, 493 U.S. 975 (1989). Furthermore, the presence of a property not possessed by the prior art is evidence of nonobviousness. *In re Papesch*, 137 USPQ 43 (C.C.P.A. 1963).

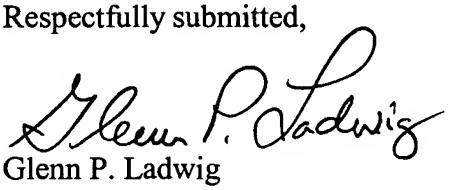
As indicated in paragraph 0014 of the subject patent application, the fact that metanicotine can protect nicotinic receptors from the inhibitory after-effects of other potentially therapeutic compounds is particularly advantageous because it means that co-administration of metanicotine with other compounds can provide a means to tune a spectrum of effects to enhance receptor subtype-selective activation, thereby providing a more positive profile of effects. The benefits of the claimed methods would not have been apparent to the skilled person from the prior art documents, individually, or in combination. Therefore, the applicants respectfully submit that the claimed invention is not obvious over the prior art. In view of the foregoing remarks, reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a) is respectfully requested.

In view of the foregoing remarks and amendments to the claims, the applicant believes that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

The applicant invites the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



Glenn P. Ladwig
Patent Attorney
Registration No. 46,853
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: Saliwanchik, Lloyd & Saliwanchik
A Professional Association
2421 NW 41st Street, Suite A-1
Gainesville, FL 32606-6669

GPL/mv
Attachments: Declaration by Dr. Papke under 37 C.F.R. §1.132
Papke *et al.* (2000) publication
Papke *et al.* (2002) publication
Kem (2000) publication